Remarks

I. The Claims

Upon entry of the foregoing amendment, claims 1, 6-13, 19 and 24-37 are pending in the application, with claims 1 and 35 being the independent claims. Claims 6, 7, 12, 13, 24-31, 34 and 35 are sought to be amended. Claim 5 is sought to be cancelled. Claims 2-4, 14-17 and 38-63 are currently withdrawn and are being maintained of record pending rejoinder or the filing of one or more divisional applications. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Support for the amendment of claim 35 can be found, *inter alia*, throughout the specification, e.g., page 1, lines 11-12; page 11, lines 26-30; page 20, lines 1-4 and 23-25; Examples 2-4, 24, and 26; and original claim 35.

Claims 6, 7, 12 and 13 are amended solely to correct for antecedent basis. Claims 24-31 are amended to change claim dependency. Claim 34 is amended to fix a typographical error.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 5-13, 19 and 24-37 were rejected under 35 U.S.C. § 112, first paragraph, because:

> the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in* vivo or *in vitro*).

(Office Action, page 2.) Applicants respectfully disagree.

The purpose of the enablement requirement is to ensure that the specification describes the invention in such terms that one skilled in the art can make and use the invention commensurate with the scope of the claims. (*E.g.*, see MPEP § 2164 (eighth edition, August 2006).) The relevant inquiry for determining whether the scope of the claims is commensurate with the specification is "whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the

claims." (*In re Moore*, 439 F.2d 1232, 1236 (CCPA 1971).) With regards to therapeutic or pharmacological utilities the MPEP states,

> [a]s a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

(MPEP § 2107.03(I); single underlining in original, double underlining added.)

Applicants believe the Examiner's basic position to be that the *in vitro* and/or *in vivo* results shown in Applicants' specification do not correlate with effective treatment results obtainable in a human. The Examiner states with regards to xenografts in mice that,

> the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen.

(Office Action, page 7; underlining added.) Applicants believe the Examiner cites the articles in the Office Action (pages 5-8) to support the position that the *in vivo* therapeutic or effective treatment results in a mouse are not predictive of results in a human.

As a preliminary matter, Applicants note that the claims, presented herein, relate to, *inter alia*, methods of reducing the viability of a hematopoietic tumor cell(s). Even though the subject matter of the present claims encompasses wherein the claimed methods would result in "the effectiveness of treating humans", there is no such "effectiveness" limitation in any of the present claims. The Examiner's rejections unfairly focus on enabling effective treatment of

humans.[1] Whether or not a therapeutic reduction of tumor cell viability can be shown or predicted is not pertinent for meeting the enablement requirement with regards to the subject matter of the invention claimed herein, since the claims do not recite any limitations directly related to a therapeutic reduction of tumor cell viability.[1]

The claims presented herein refer to, *inter alia*, methods of reducing the viability of a hematopoietic tumor cell(s) comprising administering a vesicular stomatitis virus to a hematopoietic tumor cell(s). At the time of filing, one skilled in the art, relying on the knowledge in the art and the teachings of Applicants' specification, would have been able to practice the presently claimed invention without undue experimentation, *e.g.*, *in vitro*, *ex vivo* and *in vivo*, even in a human. For example, one skilled in the art, upon review of the specification, would have been able to utilize numerous *in vitro* and *in vivo* methods for administering substances, including viruses, to a hematopoietic tumor cell(s) without undue experimentation. The present specification clearly demonstrates that a VSV virus administered to a hematopoietic tumor cell(s) would result in reducing the viability of the tumor cell(s). The Examiner has not presented any reasons or evidence to the contrary. The Examiner's rejection focuses on "extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen" (Office Action, page 7; underlining added), not on reducing the viability of a hematopoietic tumor cell(s) comprising administering a vesicular stomatitis virus to the tumor cell(s).

For completeness Applicants discuss below the articles relied on by the Examiner in the outstanding Office Action and discuss why they do not support an enablement rejection of the claims presented herein. As a general point, many of these articles actually provide support that (i) the claims are enabled and (ii) even that one skilled in the art would conclude that the *in vitro* and/or *in vivo* results in Applicants' specification and in the articles discussed in Section II.A (below) would reasonably correlate with results in other animals, such as humans. Additionally, Applicants provide herewith numerous articles related to reducing the viability of a tumor cell(s)

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[1] For clarity, Applicants believe that, if presented, similar claims requiring effective treatment of humans would be enabled by the present application.

by administering a vesicular stomatitis virus to the tumor cell(s). Several of these articles are discussed below.

Applicants' previous Reply of November 24, 2004 discussed McCormick (U.S. Patent No. 5,677,178) and Pecora (Pecora *et al.* J. of Clin. Oncol. 20(9):2251-2266 (2002)). *Inter alia*, McCormick and Pecora are presented as examples showing that viral therapy results, using *in vitro* assays and *in vivo* xenograft models, reasonably correlate with clinical results. The McCormick patent relates to ablating neoplastic cells using an E1b deleted adenoviral vector. Onyx-015 is an E1b deleted adenoviral vector that was shown to have some efficacy in human clinical trials. (*E.g.*, see Nemunaitis *et al.* Journal of Clinical Oncology, 19(2):289-298 (2001).) Pecora describes positive Phase I data using a replication competent strain of Newcastle Disease Virus. Both Pecora and McCormick demonstrate that the results from *in vitro* and *in vivo* models, described in each article, have a reasonable correlation with clinical results. The same or similar models have been utilized in Applicants' specification and in the articles provided herewith, see Section II.A below.

However, the Examiner dismisses the value of the Pecora and McCormick documents saying, "since neither McCormick nor Pecora utilize VSV to treat hematopoietic cancers, they cannot be relied upon to 'demonstrate' that *in vitro* data correlates with *in vivo* efficacy."[2] (Office Action, page 10; underlining added.) Applicants respectfully assert that these two documents are more relevant than the articles relied on by the Examiner in an attempt to support an enablement rejection. McCormick and Pecora use assays and models to test viral therapy and support the position that these models have a reasonable correlation with clinical results. Applicants could not find any passages in the articles cited by the Examiner (Office Action, pages 5-8) that even discuss assays or models with regards to viral therapy, let alone related to the utilization of VSV. In fact, most if not all of the articles relied on by the Examiner relate to small molecule drug evaluations.

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[2] Following the Examiner's logic, the references the Examiner refers to in the Office Action cannot be relied upon to "demonstrate" that *in vitro* or *in vivo* data does not correlate with clinical efficacy.

A. Evidence That Applicants' Claims Are Enabled

Applicants provide herewith the following journal articles related to reducing the viability of a hematopoietic tumor cell(s) comprising administering a VSV virus to the tumor cell(s).

(i) Lichty *et al.* (Human Gene Therapy, 15:821-831 (2004))

(ii) Césaire *et al.* (Oncogene, 25:349-358 (2006))

(iii) Porosnicu *et al.* (Cancer Research 63:8366-8376 (2003))

(iv) Balachandran and Barber (IUBMB Life 50:135–138 (2000))

(v) Stojdl *et al.* 2003 (Cancer Cell, 4:263-275 (2003))

(vi) Stojdl *et al.* 2000 (Nature Medicine, 6(7):821-825 (2000))

These articles were published subsequent to Applicants' priority filing (U.S. Patent Application No. 60/287,590, filed September 17, 1999). These articles provide evidence that at the time of Applicants' priority filing, one skilled in the art using the teachings in Applicants' specification would have been enabled to use the presently claimed methods for reducing the viability of a tumor cell(s) by administering a vesicular stomatitis virus to the tumor cell(s).

In particular, Lichty *et al.* shows, *inter alia*, the following: (1) Four distinct VSV virus strains were able to kill at least 11 of 12 cell lines in a panel of human leukemic cell lines (*e.g.*, see page 821, Overview Summary paragraph and Table 1); (2) Two VSV viruses were successfully used to purge leukemia cells from mixed cultures containing peripheral blood stem cells (see, *e.g.*, paragraph bridging page 827-828 and Table 3); and (3) VSV viruses kill myeloma cells from primary patient samples (see, *e.g.*, paragraph bridging column 1 to column 2 on page 828 and Figure 3). Therefore, Lichty *et al.* shows both (i) a reduction of viability in most, if not all, hematopoietic tumor cell types by administering a VSV virus and (ii) a reduction of viability of hematopoietic tumor cells from human patients.[3] This article also shows the selective reduction in viability of hematopoietic tumor cells (leukemic cells) in a population comprised of peripheral blood stem cells. Lichty *et al.* concludes the article by stating:

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[3] Lichty *et al.* also states, "[w]e have been struck by the extreme resistance of normal bone marrow progenitors to VSV infection . . . .it is clear that bone marrow stem cells and normal peripheral blood lymphocytes have active antiviral programs that rapidly blunt virus infections."

> [t]aken as a whole these observations and the results reported in this study point to the utility of VSV as a leukemolytic agent for the *in vivo* and *ex vivo* treatment of hematologic malignancy.

The results described in Lichty *et al.* provide, at minimum, a reasonable correlation that Applicants' claimed methods, related to reducing the viability of a tumor cell, are applicable *in vitro*, *ex vivo*, or *in vivo* (*e.g.*, in a human), especially in light of the fact that Lichty *et al.* describes results using human patient samples. Therefore, Lichty *et al.* demonstrates that Applicants' invention, as claimed herein, is enabled.

Césaire *et al.* tested four adult T-cell leukemia samples from four human patients. All four samples "underwent rapid oncolysis in a time dependent manner" upon administration of a VSV virus. (*E.g.*, see abstract and Table 1.) Additionally, a reduced viability was observed upon administration of a VSV virus to 2 of 2 HTLV-1 transformed T-cell lines and 2 of 2 B-cell chronic lymphocytic leukemia (B-CLL) cell lines.[4] (*E.g.*, see page 351, first column, last paragraph and page 353, first column, respectively.) "[N]onleukemic cells from patients with HAM/TSP [HTLV-1-associated myelopathy/tropical spastic paraparesis] were resistant to VSV infection." (Page 355, second column, underlining added.) Similar to Lichty *et al.*, Césaire *et al.* also describes results using human patient samples. Therefore, Césaire *et al.* demonstrates that Applicants' invention, as claimed herein, is enabled.

Porosnicu *et al.* shows that infection of K562 cells (human leukemia cell line) and EL4 cells (T-cell lymphoma) with 4 different VSV viruses resulted in >75% cell death within 24 hours. (*E.g.*, see page 8370, second column, first full paragraph and Figure 4). These four viruses were also tested *in vivo* in an immunocompetent mice model using A20 cells (B-cell lymphoma cells). In the present Office Action, the Examiner refers to Bibby as teaching that "in the interest of finding more clinically relevant models, orthotopic models have been developed." (Office Action, page 8.) The immunocompetent mice model using A20 cells is an orthotopic

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[4] Césaire *et al.* also tested three B-CLL and one T-CLL from patients, *ex vivo*. According to Césaire *et al.* these samples were not permissive to VSV replication. (*E.g.*, see page 353, first column and Table 1.) However, Césaire *et al.* states, "[t]his discrepancy in VSV oncolysis may be due to the fact that CLL cells do not proliferate but remain in G_0 *ex vivo* (Meinhardt *et al.*, 1999; Caligaris-Cappio, 2003)." (Page 357, second column.)

model, which in Porosnicu *et al.* demonstrated a significant reduction of *in vivo* tumor growth for each of the four VSV viruses as compared to the control groups. (*E.g.*, see page 8371, column1 and Figure 5.)

Balachandran and Barber show that 4 of 4 hematological malignancies tested had their viability reduced by administration of a VSV virus. Balachandran and Barber state:

> [t]o further examine the ability of VSV to induce cell death in other transformed human cell lines, including those derived from . . . various cells derived from hematological malignancies (HL 60, K562, Jurkat, BC-1), we infected those cells with VSV as described in Experimental Procedures. We observed that VSV efficiently replicated and induced cytolysis of every established cell line tested.

(Page 136, paragraph bridging columns 1 and 2; underlining added.)

Stojdl *et al.* 2003 also screened a panel of leukemia cell lines and found that 4/6 cell lines tested were deemed highly sensitive to wild-type VSV virus infection, *e.g.*, see Table 2A.

Stojdl *et al.* 2000 shows that three "acute myelogenous leukemia (AML) cell lines OCI/AML3, OCI/AML4 and OCI/AML5 were very susceptible to VSV infection". (*E.g.*, see page 822, column 2.) Additionally, this article shows that VSV had selective oncolytic properties in a co-culture of leukemic OCI/AML3 cells mixed with normal human bone marrow cells (at a ratio of 1:9). (*E.g.*, see page 22, column 2, first sentence.)

The articles discussed in this section provide clear evidence that the viability of hematopoietic tumor cells, in general, are reduced upon administration of a vesicular stomatitis virus. Additionally, these articles demonstrate that the claims, as presented herein, are enabled.

B. Examiner's Citations Do Not Support an Enablement Rejection

Kelland (Eur. J. Cancer. 2004, 40(6):827-836)

The Examiner briefly summarizes Kelland (Office Action, pages 5-6), but does not relate or compare the statements in Kelland to Applicants' claimed invention. Therefore, Applicants are not able to specifically address Kelland with regards to the current enablement rejection of the present claims.

On the other hand, Kelland (Eur. J. Cancer. 2004, 40(6):827-836), which is cited by the Examiner, provides various rationale which supports the premise that the *in vitro* and *in vivo* results in Applicants' specification and in the articles discussed above are predictive of results in a human.

Kelland provides analyses that indicate whether or not human tumor xenograft models might be predictive of clinical results. Kelland summarizes this analysis on page 831, first column, stating:

> [o]verall, taking all of the above into consideration, one may reasonably conclude that, at least for cytotoxic cancer drugs, the human tumour xenograft model, is a good predictor of clinical activity.

(Kelland, page 831, first column; underlining added). VSV viruses can reduce the viability of a tumor cell, *inter alia*, via cytotoxic effects. Therefore, successful results are a "good predictor of clinical activity" and demonstrate that the claims, as presented herein, meet the requirements for enablement. Kelland goes on to state that,

> [i]n careful mechanism-based studies, combined with sound pharmacological principles (as described above), then, in my view, the xenograft model remains of great value, both for assisting in the selection of leads for clinical evaluation and for guiding clinical studies.

(Kelland, page 833, second column.) Although not wishing to be bound by theory, Applicants' specification provides possible mechanisms related to the claimed methods. For example, differential susceptibility of a tumor cell to a VSV virus can be more pronounced in the presence of interferon. Also, differential susceptibility of a tumor cell to a VSV virus can be related to, *inter alia*, the PKR status of a tumor cell. Some, if not all, of the *in vitro* and *in vivo* studies described in the present application and in the articles described above (Section II.A) may be considered as mechanism-based studies and, according to Kelland, are therefore of assistance in guiding clinical studies.

In summary, Kelland clearly supports the position that one skilled in the art would conclude that the models and related results, described in Applicants' specification and in the articles cited above, reasonably correlate with an expected similar result in other animals, such as humans.

Wang et al. (Exp. Opin. Biol. Ther. 2001, 1(2):277-290)

Applicants are unclear as to the relevance of this article with regards to the presently claimed invention. Wang *et al.* relates to T-cell-directed cancer vaccines, whereas the claimed invention relates to methods of reducing the viability of a hematopoietic tumor cell(s) comprising administering to the hematopoietic tumor cell(s) a VSV virus.[5] Therefore, Applicants do not understand the relevance of the sections of Wang *et al.*, referred to by the Examiner, to the subject matter of the claims as presented herein. Additionally, the Examiner has not described how the disclosure of Wang *et al.* relates to the results in Applicants' specification or to the presently claimed invention.

Gura (Science, 1997, 278:1041-42)

Gura discusses historical results in a general and broad sense. Applicants' presently claimed methods relate to, *inter alia*, reducing the viability of a hematopoietic tumor cell(s), comprising administering to the tumor cell(s) a VSV virus. Gura does not speak to the predictive value of models related to evaluating the administration of a virus to a tumor cell. Therefore, Guru bears little, if any, relevance to the presently claimed invention or related *in vitro* or *in vivo* experiments.

Voskoglou-Nomikos et al. (Clin. Cancer Res. 2003 9:4227-4239)

Again, the Examiner has not related the disclosure in Voskoglou-Nomikos *et al.* to the claims as presented herein. The Examiner states that "xenograft models were only predictive for non-small cell lung [cancer] and ovarian cancers, but not for breast and colon cancers". (Office Action, page 6.) Voskoglou-Nomikos *et al.* appears to be silent with regards to predictability of the xenograft models related to the administration of a VSV virus to a hematopoietic tumor cell. Also, Voskoglou-Nomikos *et al.* suggests predictability can vary with specific models. Therefore, Voskoglou-Nomikos *et al.* provides no evidence as to whether *in vitro* or *in vivo*

[5] Although, Applicants acknowledge that *in vivo* the immune system may contribute to reducing the viability of a tumor cell.

experiments related to administering a VSV virus to a hematopoietic tumor cell(s) reasonably correlate to expected results in other animals, such as humans.

Saijo et al. (Cancer Science 2004, 95(10):772-776)

> The Examiner indicates that,
>
> Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract).

(Office Action, pages 6-7; underlining added.) Most negative phase III results do not prove statistical inactivity. Instead these "negative" results only indicate that a certain degree of activity has not been met in the clinic for the sample size tested. Even Saijo admits finding active drugs in the clinic are often hampered by having extremely small sample sizes (*e.g.*, see page 774; second column). Economic factors come into play when determining sample sizes. Of course, typically drugs that have "strongly positive" results will allow for a phase III trial to be successful with a small sample size. However, the present claims do not require "strongly positive" results.

Applicants note that Saijo focuses on whether the results of preclinical studies for molecular-target-based drugs correlate with results seen in clinical trials. Applicants do not consider the disclosure of Saijo to have particular relevance to methods of reducing the viability of a hematopoietic tumor cell(s) comprising administering to the tumor cell(s) a VSV virus. As noted herein, Voskoglou-Nomikos *et al.* suggests predictability can vary with specific models.

Schuh (Toxicologic Pathology 2004, 32(Suppl. 1):53-66)

Schuh states "common reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure rates; seldom duplicated in clinical trials." (Abstract; underlining added.) As Applicants show herein, administration of VSV virus in several mouse models using hematopoietic tumor cell types resulted in reducing the viability of the hematopoietic tumor cells. Therefore, one skilled in the art would expect these results to reasonably correlate with results expected in a human.

Bibby (Eur. J. Cancer 2004 40(6):852-857)

The Examiner refers to Bibby as teaching that "in the interest of finding more clinically relevant models, orthotopic models have been developed." (Office Action, page 8.) Bibby discusses whether to use orthotropic models, for example, as opposed to some xenograft models. However, Bibby does not teach that results in xenograft models do not reasonably correlate with clinical results in another animal or a human. In fact with regards to a hematopoietic cell(s), Bibby states:

> In the past, murine tumour systems were used for drug screening with mouse leukaemias being utilised as prescreens [1]. These grew very rapidly, had a high growth fraction and proved to be sensitive to a number of agents that were subsequently shown to have more activity against leukaemias and lymphomas than against solid carcinomas and sarcomas and to be toxic to the bone marrow [2]. As a result of these early screens, there is a general misconception that tumours in rodents are sensitive to drug therapy and are easy to cure. In reality this is untrue and back in 1987 Corbett and colleagues [3] pointed out that most of the agents that had entered the clinic at that time had poor or no activity against the majority of transplantable solid tumours in mice. Modest activity is often seen, but this is usually at the expense of host toxicity [4].

(page 852.) Bibby clearly stands for the proposition that with regards to leukemias "there is a general misconception that tumours in rodents are sensitive to drug therapy and are easy to cure" and that "[m]odest activity is often seen." Therefore, one skilled in the art would conclude that methods resulting in the reduction of the viability of a hematopoietic tumor cell(s) in a rodent would reasonably correlate with results obtained in a human.

Peterson et al. (Eur. J. Cancer 2004 40:837-844

Peterson *et al.* discusses methods that might improve the predictability of results in a xenograft model. Peterson *et al.* does not teach that results in xenograft models do not reasonably correlate with clinical results in another animal or a human. Therefore, Applicants are unclear as to the relevance of Peterson to the subject matter of the claims presented herein.

C. Summary

In summary, Applicants assert that one skilled in the art, upon review of Applicants' specification, would have been enabled at the time of filing to reduce the viability of a hematopoietic tumor cell(s) without undue experimentation, even in an individual such as a human using methods that are the subject matter of the claims presented herein. In addition, Applicants have discussed in Section II.A (above) articles that provide further evidence that following the teachings of Applicants' specification one skilled in the art at the time of filing would have been able to reduce the viability of a hematopoietic tumor cell(s) comprising administering a vesicular stomatitis virus to a tumor cell(s). Furthermore, based on the principles of the articles cited by the Examiner and as discussed above, the *in vitro* and *in vivo* results presented in Applicants' specification and in the articles discussed in Section II.A (above) demonstrate that one skilled in the art would conclude that these results will reasonably correlate with results expected in other animals (including humans) with respect to reducing the viability of a hematopoietic tumor cell(s) comprising administering a vesicular stomatitis virus to a tumor cell(s).

Even though the evidence presented herein conclusively supports that the claimed invention meets the enablement requirements, Applicants remind the Examiner that "[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05; underlining in original.)

In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

III. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 5-13, 19 and 24-37 were rejected "under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". (Office Action, page 11.) Applicants respectfully disagree.

A. Claim 1

The Examiner states that claim 1 is "rendered vague and indefinite by the use of the phrase 'administering to the tumor cell a virus'".[6] (Office Action, page 12.) Applicants respectfully disagree.

The MPEP states, "[t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.' *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576". (MPEP § 2173.02 at 2100-212.)

The Examiner states, "[c]laim 1 recites the phrase 'administering to **the** tumor cell **a** virus . . . It is unclear how this is accomplished when said cell resides (and circulates) within an individual." (Office Action, page 12.) Applicants respectfully disagree.

One skilled in the art is well aware of numerous methods for administering a substance, such as a virus, to a cell that resides and/or circulates within an individual. As an example, doctors routinely provide substances (*e.g.*, drugs including biologics) to individuals, wherein the substances are delivered to a particular cell. This includes cells that reside and/or circulate within an individual. Therefore, there are clearly numerous methods known for administering a VSV virus to a hematopoietic tumor cell(s) that resides and/or circulates within an individual. Additionally, Applicants respectfully submit that the Examiner has not put forth reasons why the subject matter of claim 1 would be unclear to one skilled in the art and has only made a conclusory statement that it is unclear how administering is accomplished. (Office Action, page 12.)

Applicants assert that one skilled in the art would understand what is claimed and that the scope of the claimed subject matter of claim 1 would be readily apparent to one of ordinary skill in the art. Further, a person of ordinary skill in the art who is doing something to a

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[6] Applicants assume that claims 5-13, 19 and 25-34 are rejected under 35 U.S.C. § 112, second paragraph, solely because they depend (directly or indirectly), from claim 1. Additionally, Applicants assume that claims 35-37 are rejected under 35 U.S.C. § 112, second paragraph, for reciting the phrase "administering a vesicular stomatitis virus". If the Examiner maintains the rejections under 35 U.S.C. § 112, second paragraph, Applicants respectfully request clarification.

hematopoietic tumor cell(s) with a VSV virus, *in vitro* or *in vivo*, would have no difficulty determining whether he is administering a VSV virus to the tumor cell(s).

B. Claim 24

The Examiner states that claim 24 is "rendered vague and indefinite by the use of the phrase 'administering interferon to the tumor cell'". (Office Action, page 12.) Applicants respectfully disagree.

Applicants refer the Examiner to the reasons in Section III.A as they may apply to this rejection. Applicants assert that one skilled in the art would understand what is claimed and that the scope of the claimed subject matter of claim 24 would be readily apparent to one of ordinary skill in the art. In fact, various interferons are approved by the FDA, *inter alia*, for the treatment of leukemia. Clearly the treatment of leukemia involves administration to a tumor cell that resides and/or circulates in an individual.

In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. § 112, second paragraph.

C. Request for Suggested Claim Language

The MPEP states,

> Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.

(MPEP § 2173.02 @ 2100-211.) If the Examiner maintains the rejections under 35 U.S.C. § 112, second paragraph, Applicants would appreciate the Examiner suggesting claim language that he considers acceptable.

IV. Toxicity in PKR-/- Mice

Applicants would like to clarify a point. The Examiner states, "high toxicity (*i.e.*, lethal toxicity) is indicative of a lack of efficacy (as is the case with the intravenous administration of VSV to PKR-/- mice[])." (Office Action, page 11.) To clarify the record, Applicants note that toxicity in PKR-/- mice in no way should be interpreted as correlating with levels of toxicity in

other animals such as humans. The PKR status of cancer cells and normal cells with relation to VSV infection is discussed in Applicants' specification, *e.g.*, see page 11, lines 8-15. In most cases, cells that exhibit reduced, or no PKR activity are susceptible to viral attack and exhibit cancerous growth. Typically, normal cells will exhibit PKR+/+. The PKR-/- mouse strain was used to demonstrate the relation of the PKR status of a cell to the cell's ability to resist VSV infection, *e.g.*, see Example 13 of Applicants' specification.

Conclusion

It is not believed that extensions of time are required beyond those that may otherwise be provided for herein or in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, The United States Patent and Trademark Office is hereby authorized to charge any fee deficiency required to prevent abandonment of the current application or credit any overpayment to Deposit Account 50-1677.

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: August 2, 2007